centrated hydrochloric acid was added and the refluxing was continued for 2 hours more. Most of the hydrochloric acid was removed under reduced pressure, 50 ml. of water was added and the solution was filtered to remove insoluble tar. The filtrate was brought to a *p*H of 4 with concentrated ammonium hydroxide and allowed to stand overnight in the refrigerator. The brown precipitate which formed was removed by filtration, washed with 95% ethanol and ether and redissolved in dilute sulfuric acid. Neutralization with ammonium hydroxide gave 0.6 g. (22%) of *dl*-thyronine as a tan powder which melted with decomposition at 255–257°.

Preparation of *dl*-Thyronine from Compound III *via* Compound XII. Hydrolysis.—A solution of 8.88 g. (0.02 mole) of diethyl 4-(4′-nitrophenoxy)-benzylacetamidomalonate (III) in a mixture of 200 ml. of 95% ethanol, and 200 ml. of concentrated hydrochloric acid was refluxed for 12 hours. The solution was concentrated by distillation to remove the alcohol, and water was added to dissolve the precipitated amino acid hydrochloride. This solution was filtered free of a trace of insoluble material and brought to *p*H 4 with concentrated ammonium hydroxide. When the cloudy solution was cooled overnight in the refrigerator, 5.4 g. (90%) of white needles were deposited, m.p. 187–188°. The product is evidently α-amino-β-[4-(4′-nitrophenoxy)-phenyl]-propionic acid (X).

Benzoylation.—A solution of 3.02 g. (0.01 mole) of this substance and 0.4 g. (0.01 mole) of sodium hydroxide in 100 ml. of water was cooled to 5° in an ice-bath. Alternate additions of 10% aqueous sodium hydroxide and benzoyl chloride were made until 12.0 ml. (0.03 mole) of the sodium hydroxide solution and 3.2 ml. (0.03 mole) of the acid chloride had been added. The solution was stirred for 30 minutes, filtered and acidified with concentrated hydrochloric acid. The resulting precipitate was thoroughly extracted with low-boiling (30–60°) petroleum ether to remove benzoic acid, then was crystallized from 95% ethanol to give 2.44 g. (60%) of white needles melting at 91–92°, evidently α-benzamido-β-[4-(4′-nitrophenoxy)-phenyl]-propionic acid (XI).

Reduction.—To a solution prepared from 4.06 g. (0.01 mole) of the above product, 200 ml. of water and 4.0 g. (0.1 mole) of sodium hydroxide was added 25 g. (0.09 mole) of hydrated ferrous sulfate in 100 ml. of water. The resulting suspension was heated on a steam-bath for 1 hour and filtered while hot. The ferric hydroxide collected was washed with 50 ml. of hot water and the combined filtrate was acidified with glacial acetic acid. A white powder was deposited when the cloudy solution was allowed to stand overnight in the refrigerator. This was dissolved in 200 ml. of hot 1% hydrochloric acid and the solution was filtered while hot, then brought to *p*H 4 by addition of concentrated ammonium hydroxide. When the solution was cooled, 3.1 g. (80%) of a white powder was deposited, m.p. 181–182°, which was evidently α-benzamido-β-[4-(4′-aminophenoxy)-phenyl]-propionic acid (XII).

Diazotization and Hydrolysis.—A solution of 3.76 g. (0.01 mole) of the above product in 200 ml. of water containing 5 ml. of concentrated hydrochloric acid was cooled to 10° and 0.8 g. (0.012 mole) of sodium nitrite was added with stirring. The solution was allowed to stand at room temperature for 2 hours, filtered to remove the small amount of insoluble material and refluxed for 3 hours. The volume of the solution was then reduced to 50 ml. by distillation, an equal volume of concentrated hydrochloric acid was added and the mixture was refluxed for 4 hours. Most of the hydrochloric acid was removed under reduced pressure, 50 ml. of water was added and the solution was filtered to remove the insoluble tar. The filtrate was neutralized with concentrated ammonium hydroxide and allowed to stand overnight in the refrigerator. The precipitate which formed was removed by filtration and washed with 95% ethanol and ether to give 0.8 g. (30%) of *dl*-thyronine as a tan powder melting at 251–254° with decomposition. Dissolving the powder in dilute sulfuric acid and precipitating with ammonia raised the m.p. to 256–257°.

Conversion of 4-Aminodiphenyl Ether into 4-Hydroxydiphenyl Ether.—A solution of 1.5 g. (0.022 mole) of sodium nitrite in 200 ml. of water was added to a cold solution of 3.7 g. (0.02 mole) of 4-aminodiphenyl ether[16] in 150 ml. of water containing 10 ml. of concentrated hydrochloric acid. The solution was stirred for 15 minutes with the temperature remaining below 10°, and 5.5 g. (0.025 mole) of 40% fluoboric acid solution was added. The precipitate which formed was allowed to settle for 15 minutes, removed by filtration and air dried. The dry white powder was added to 150 ml. of hot glacial acetic acid and the red solution was refluxed for 1 hour. The acetic acid was removed under reduced pressure and the red residue was dissolved in 100 ml. of 95% ethanol containing 3.0 g. of potassium hydroxide. The solution was refluxed for 1 hour, the ethanol was distilled away and the residue was dissolved in 50 ml. of water. The solution was filtered to remove the small amount of insoluble material and the filtrate was acidified with hydrochloric acid. The brown precipitate which formed was crystallized from hot water to give 2.5 g. (67%) of white needles melting at 81–82°. Another crystallization raised the m.p. to 83–84°. Osterlin[17] reported a m.p. of 84° for this compound.

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[16] Prepared from 4-nitrodiphenyl ether by reduction with zinc dust and calcium chloride in an ethanol–water solution. See C. M. Suter, THIS JOURNAL, **51**, 2581 (1929).

[17] M. Osterlin, *Monatsh.*, **57**, 31 (1931).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

Betaine Esters. A Study of their Reactions[1]

BY WERNER V. COHEN[2] AND ALSOPH H. CORWIN

RECEIVED JUNE 3, 1953

In betaine esters, the effect of the formal positive charge is not sufficient to cause the loss of a proton from the methylene group in alkaline solutions. It is sufficient, however, to bring about alkyl–oxygen bond fission in the ester group. This reaction is reversible so that esterification can be accomplished by the action of alcohol on the sodium salt of the betaine. Identification of certain betaine salts is complicated by the fact that they form molecular complexes with sodium and potassium bromide.

It has been recognized that loss of a proton from a methylene group can be promoted either by electron attracting substituents or by unsaturated groups capable of yielding double resonance in the ion of the conjugate base. Earlier work indicates that the resonance effect may be of the greater importance. In order to learn how the proximity of a formally charged nitrogen atom will modify the chemistry of neighboring methylene and carbalkoxy groups we have investigated the chemistry of certain betaine esters of type I.

Betaine esters may be compared to esters of sulfuric and sulfonic acids in that there exists an essentially positive charge distribution around the hetero-atoms in both classes of compounds. In the betaine esters, however, the charge is separated

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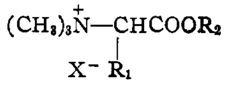
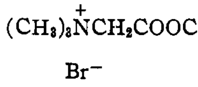
[1] From the doctoral dissertation of Werner V. Cohen, The Johns Hopkins University.

[2] United States Public Health Service Research Fellow 1950–1951.



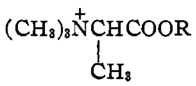
$$\underset{X^-}{(CH_3)_3\overset{+}{N}}-\underset{R_1}{\underset{|}{C}}HCOOR_2$$

I, R_1, R_2 = alkyl groups



$$\underset{Br^-}{(CH_3)_3\overset{+}{N}CH_2COOC_2H_5}$$

II



$$(CH_3)_3\overset{+}{N}\underset{CH_3}{\underset{|}{C}}HCOOR$$

III

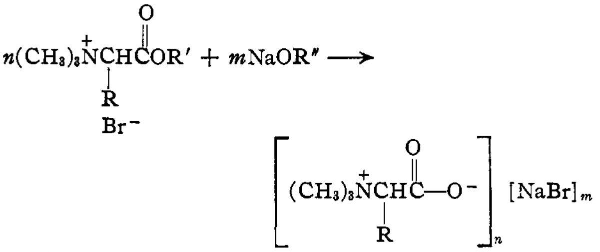
from the alkoxy group by intervening carbon atoms. Alkyl sulfates and sulfonates differ from carboxylic esters in one important respect. While the former are distinguished by the ease with which their alkyl–oxygen bond is broken, the latter undergo this type of cleavage only very rarely, reactions involving the acyl–oxygen bond being the rule.[3] In the few reported instances of alkyl–oxygen bond fission in carboxylic esters drastic reaction conditions are required to achieve this unusual result.[4]

In the case of betaine esters it is not at once obvious whether these compounds are more closely related in their reactions to other carboxylic esters or whether, because of their peculiar charge distribution, they would more closely resemble the sulfuric esters.

Information on the relative reactivity of the carbon–oxygen bonds in the ester group of betaine esters was sought by reaction of equimolecular amounts of carbethoxymethyl trimethylammonium bromide (II) and sodium methoxide at room temperature in specially dry alcohol. An immediate reaction occurred with precipitation of a crystalline material whose composition was the same no matter whether the reaction was carried out in methyl, ethyl, benzyl or *t*-butyl alcohol. The usual ester exchange reaction of carboxylic esters with alkoxides did not take place.

Changing the alcoholic portion of II from an ethyl to a methyl group did not alter the composition of the precipitate, while changing the acid portion from glycine betaine to alanine betaine as in III resulted in a different material.

The precipitates were identified as molecular complexes of anhydrous betaines with sodium bromide IV. Their composition is variable and similar to that of the water-containing complexes described by Anslow and King.[5] From concentrated equimolecular solutions of glycine betaine hydrobromide and sodium hydroxide in dry ethanol crystalline complexes were obtained by the addition of ether, which contained more than one mole of anhydrous betaine for each mole of sodium bromide V and proved to be identical with those arising from the ester II as indicated above.

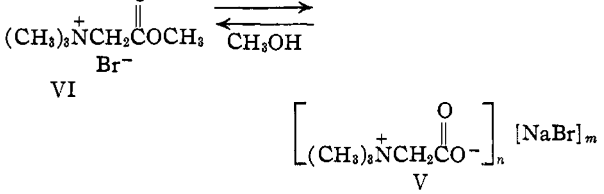


$$n(CH_3)_3\overset{+}{N}\underset{\underset{Br^-}{R}}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}OR' + mNaOR'' \longrightarrow \left[(CH_3)_3\overset{+}{N}\underset{R}{\underset{|}{C}}H\overset{O}{\overset{\|}{C}}-O^-\right]_n [NaBr]_m$$

R,R′ = alkyl, H

IV

The break-down of betaine ester II into the corresponding alkali salt could be reversed by treating dry methanol with the sodium bromide–glycine betaine complex V. Carbomethoxymethyltrimethylammonium bromide (VI) was obtained.



$$\underset{Br^-}{(CH_3)_3\overset{+}{N}CH_2\overset{O}{\overset{\|}{C}}OCH_3} \underset{CH_3OH}{\overset{NaOR}{\rightleftarrows}} \left[(CH_3)_3\overset{+}{N}CH_2\overset{O}{\overset{\|}{C}}O^-\right]_n [NaBr]_m$$

VI

V

The reversibility of this last reaction implies that reactions take place at the alkyl–oxygen bond in either direction. An earlier observation by Biilman that alanine betaine could be esterified by alkyl halides in cases where acid catalyzed esterification with alcohol, involving severance of the acyl–oxygen bond, had failed completely, now finds its natural explanation in the great reactivity of the free oxygen bond of betaines.[6]

As in the case of the monocarboxylic betaine esters described above it was found that dicarboxylic esters possessing a quaternary ammonium group also undergo alkyl–oxygen bond fission in basic solutions. Biscarbethoxymethyltrimethylammonium bromide (VII), for example, gave an equimolecular complex of the betaine VIII with potassium bromide when treated with one equivalent of potassium metal in dry ethanol.

The free betaine VIII was isolated as a hygroscopic salt which could not be converted into the corresponding hydrohalide by the addition of cold mineral acid, since decarboxylation with formation of II occurred too readily.

Transformation of compound VII into either VIII or IX is easily achieved by the addition of strong base to a concentrated solution of the starting ester. One equivalent of alkali hydroxide, alkoxide or carbonate will result in VIII, while two equivalents or more will produce IX. The formation of the mono- and dialkali salts with alkoxide ions affords clear evidence of a metathetic alkyl–oxygen fission and it may be presumed that a similar mechanism operates in aqueous media.

It was possible to demonstrate the existence of the diacid base IX in basic aqueous solutions, although the corresponding dicarboxylic acid X could not be prepared because of its great instability. This last mentioned acid decarboxylates with

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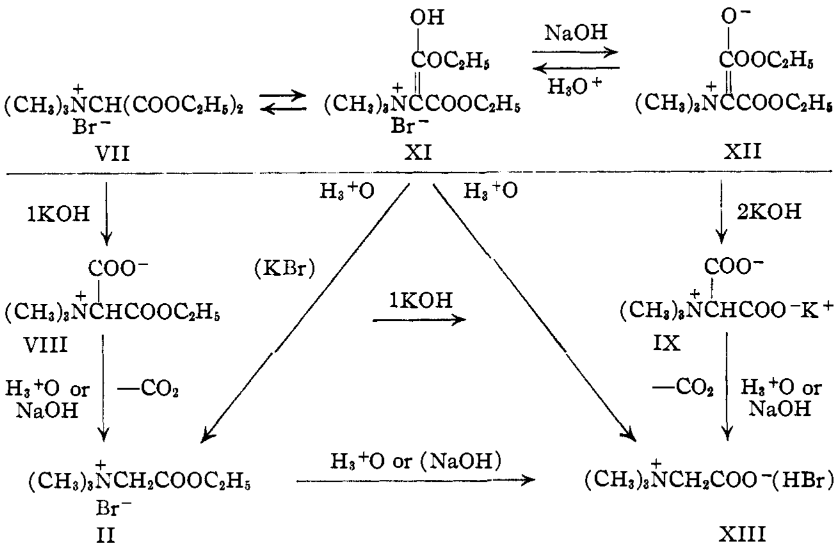
[3] L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, p. 354, *et seq.*

[4] (a) R. Willstätter, *Ber.*, **35**, 584 (1902); (b) R. Willstätter and W. Kahn, *ibid.*, 2757; (c) L. P. Hammett and H. L. Pfluger, THIS JOURNAL, **55**, 4079 (1933); (d) H. King and E. V. Wright, *J. Chem. Soc.*, 1168 (1939); (e) F. Adickes, S. von Muellenheim and W. Simson, *Ber.*, **66**, 1904 (1933); (f) A. Magnani and S. M. McElvain, THIS JOURNAL, **60**, 813 (1938); (g) C. O. Guss and L. H. Jules, *ibid.*, **72**, 3462 (1950); (h) L. F. Fieser and H. Heymann, *ibid.*, **64**, 376 (1942); (i) K. W. Wilson, J. D. Roberts and W. G. Young, *ibid.*, **71**, 2019, 2021 (1949); (j) L. P. Kuhn, *ibid.*, **71**, 1575 (1949); (k) M. P. Balfe, E. A. W. Downer, A. A. Evans, J. Kenyon, R. Poplett, C. E. Saerle and A. L. Tarnoky, *J. Chem. Soc.*, 797 (1946); (l) A. R. Olson and R. J. Miller, THIS JOURNAL, **60**, 2687 (1938); (m) J. Kenyon, S. M. Partridge and H. Phillips, *J. Chem. Soc.*, 85 (1936).

[5] W. K. Anslow and H. King, *Biochem. J.*, **22**, 1263 (1928).

[6] E. Biilman and N. Berg, *Bull. soc. chim.*, [5] **1**, 1645 (1934).

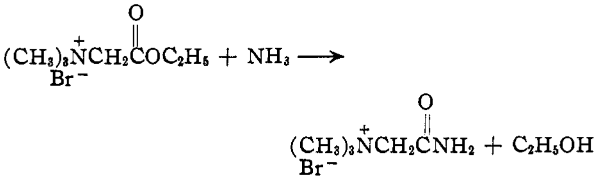
REACTIONS OF BETAINE ESTERS



mineral acids with the result that only glycine betaine hydrohalides can be isolated from its acid solutions.

$$(CH_3)_3\overset{+}{N}CH(COOH)_2 \qquad X$$

While the inductive influence of the charged nitrogen atom appears to reverse the relative importance of the two reactive sites in the carboxy and carbalkoxy groups of betaines and their esters toward basic reagents, it nevertheless can be shown that reactions are possible at the less favored acyl–oxygen bond. Thus by treating carbethoxymethyltrimethylammonium bromide II with liquid ammonia the corresponding amide was formed quantitatively in a reaction, which must have involved the acyl–oxygen bond of the ester.



$$\underset{Br^-}{(CH_3)_3\overset{+}{N}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5 + NH_3 \longrightarrow \underset{Br^-}{(CH_3)_3\overset{+}{N}}CH_2\overset{O}{\overset{\|}{C}}NH_2 + C_2H_5OH$$

To throw light on the effect of the formally charged nitrogen on the ease of enolization in mono- and dicarboxylic betaine esters, these esters were studied in dilute hydroxide solution. Concentrated hydroxide solutions could not be employed, because the slow enolization reaction under investigation was then superseded by almost instantaneous hydrolysis as described above.

In a dilute aqueous solution of the ester VII it was easy to demonstrate by potentiometric means that this is a system which slowly enolizes in a reversible manner. The enolic form of the ester ionizes, so that the temporary buffer action of the solution upon the addition of either acid or base is readily explained. The very gradual change in pH in either direction, depending on whether acid or base has been added, can be readily followed on a pH meter. The experimental data are consistent with a system in which compound VII is in equilibrium with a very small amount of a highly ionized enolic compound XI. Only very little of VII was lost through hydrolysis in 0.01 N hydroxide solution. On the other hand, compound II, the corresponding monocarboxylic betaine ester to VII, hydrolyzes so rapidly under these same conditions that its enolization could not be studied. Biilman, observing this same excessive reactivity of II toward hydroxide ions, was able to show that slow enolization of the monocarboxylic ester does, indeed, take place in alcoholic solution, if bases weaker than hydroxide are employed for the study.[6]

Efforts to prepare a stable crystalline enol betaine XII similar to that prepared from the pyridinium analog of VII[7] were unsuccessful.

From the preceding results one may infer that a trimethylammonium group as a substituent does not possess the stabilizing effect on the enol betaine that is shown by the pyridinium group. The trimethylammonium group does, however, activate the methylene group of betaine esters appreciably in as much as the corresponding unsubstituted mono- and dicarboxylic esters enolize much less readily than do the betaine esters. The magnitude of the activating effect is very much smaller than that exhibited by vicinal substituents which give rise to double resonance in the ion, *e.g.*, carbonyl groups. A charged resonating substituent such as the pyridinium group must therefore exert a more potent effect than the trimethylammonium group, which acts only by its induction.

In agreement with earlier investigators[8] it must, therefore, be concluded that increased tautomerization of the "acid" structure of a compound and particularly the extent of resonance stabilization of its conjugate base are the determining factors in deciding the reactivity of a methylene group. The purely inductive effect of the quaternary ammonium group, while of subordinate importance in promoting the formation of a carbanion is critical in bringing about alkyl–oxygen fission.

One of the authors (W.V.C.) wishes to express his appreciation of a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

Experimental

Sodium Carboxymethyltrimethylammonium Bromide (V).—To a solution of carbethoxymethyltrimethylammonium bromide (II) (5 g.) in dry ethanol (40 ml.) an equimolar amount of sodium dissolved in dry ethanol (20 ml.) is added at room temperature, with exclusion of moisture. A colorless non-hygroscopic salt settles out almost immediately (3.4 g.). It is only slightly soluble in ethanol and decomposes with evolution of a gas between 273–280°, depending on the rate of heating. The needle or plate-shaped crystals give a neutral solution in water.

The original reaction mixture remains basic for days and still contains some starting ester, which indicates that the

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(7) F. Kröhnke, *Ber.*, **70B**, 543 (1937).

(8) D. Vorlaender, *ibid.*, **52**, 269 (1917); (b) F. Kröhnke and W. Heffe, **70B**, 864 (1937); **73B**, 310 (1940); (c) H. E. Carter and D. B. Melville, *J. Biol. Chem.*, **133**, 109 (1940).

reaction does not go to completion. Addition of hydrobromic acid to a solution of V yields only glycine betaine hydrobromide, which decomposes at 213.5° (lit. value 233° (4 g.)).

Anal. Calcd. for $C_5H_{12}O_2NBr$: acid equiv., 198.1; Br, 40.35. Found: acid equiv., 199.1; Br, 40.39.

Sodium Methyl Carboxymethyltrimethylammonium Bromide.—The preparation of this compound is similar to that of V, compound III being the starting ester here. The needle-shaped hygroscopic crystals melt at 211–212° and dissolve in hot ethanol. Elemental analyses and residue determinations reveal the non-homogeneity of the sodium salt. Sodium is present to the extent of only 70–90% of the expected amount, so that more than one molecule of alanine betaine crystallizes per molecule of sodium bromide.

The corresponding hydrobromide prepared from III with silver oxide and hydrobromic acid is hygroscopic and decomposes at 183–184° with evolution of a gas.

Anal. Calcd. for $C_6H_{14}NO_2Br$: Br, 37.68. Found: Br, 37.51.

Formation of Carbomethoxymethyltrimethylammonium Bromide (VI) from V.—The sodium salt V (6 g.) was reacted with methanol in concentrated solution. After reacting for several days in the cold the ester VI was obtained (4 g.) together with some unreacted starting material. The ester VI melted at 182–183° (lit. 182–183°).

Biscarbethoxymethyltrimethylammonium Bromide (VII). Anhydrous trimethylamine (4.95 g.) was added slowly to a solution of freshly distilled ethyl bromomalonate (20 g.) in 30 ml. of dry toluene. The reaction was carried out at −10° in a pressure bottle. When the exothermic reaction had subsided, the mixture was allowed to attain room temperature overnight. The yield of colorless needle-shaped crystals, recrystallized from acetone, was 23.3 g., *i.e.*, 93%, m.p. 122–123° after drying over phosphorus pentoxide.

Anal. Calcd. for $C_{10}H_{20}NO_4Br$: C_2H_5O, 30.22. Found: C_2H_5O, 30.15, 30.23.

The corresponding chloride was prepared similarly to the bromide above. The needle-shaped hygroscopic crystals of the chloride after recrystallization from acetone melted between 88 and 108° depending on the time of drying over phosphorus pentoxide. The material could not be obtained free from impurities which probably consisted of the compound IX, the acetone-insoluble ethyltrimethylammonium chloride being absent after recrystallization. From the concentrated solution of the impure chloride the chloroplatinate, dec. 183°, and the chloroaurate, m.p. 81°, could be prepared.

Anal. Calcd. for $C_{20}H_{40}N_2O_8PtCl_6$: C_2H_5O, 21.38. Found: C_2H_5O, 21.30. Calcd. for $C_{10}H_{20}NO_4AuCl_4$: C_2H_5O, 16.17. Found: C_2H_5O, 15.99.

Potassium Carbethoxy-(carboxymethyl)-trimethylammonium Bromide (VIII).—The ester VII (7 g.) was slowly added to an equimolecular amount of potassium metal dissolved in 20 ml. of dry ethanol. The reaction was carried out with constant stirring under anhydrous conditions. After heating the mixture for two hours, potassium bromide was filtered from the cold neutral solution, which gave a very hygroscopic precipitate when dry ether was added to it. This precipitate melts at 145–146° and is insoluble in acetone in contrast to the starting material.

Anal. Calcd. for $C_8H_{15}NO_4$, KBr: C_2H_5O, 14.65. Found: C_2H_5O, 14.80.

Compound VIII loses carbon dioxide readily in acid solution. Thus, after converting the bromide into the chloride with silver chloride, the addition of chloroplatinic or chloroauric acid results in the formation of the precious metal salts of the ester II. The chloroplatinate decomposes at 215° (lit. 221°[4h]), while the chloroaurate melts at 132° (lit. 133°[9]).

Anal. Calcd. for $C_7H_{16}NO_2PtCl_6$: C_2H_5O, 12.85. Found: C_2H_5O, 12.85, 12.72. Calcd. for $C_7H_{16}NO_2AuCl_4$: C_2H_5O, 9.24. Found: C_2H_5O, 9.11.

The hygroscopic sodium analog of VIII was prepared similarly to VIII itself, m.p. 144–145°. On hydrolysis with one equivalent of base in moist alcoholic sodium hydroxide solution, it decomposes completely into sodium carbonate, glycine betaine and sodium chloride. These products prove the identity of the sodium analog of VIII, since neither VII nor II yields sodium carbonate on alkaline hydrolysis with one molar equivalent of base.

The potassium-free betaine of VIII can be prepared from VII with one equivalent of silver carbonate in aqueous solution. Silver bromide is removed by filtration and the acetone-soluble betaine is isolated by total evaporation *in vacuo* at room temperature. Like VIII the betaine in the free state loses carbon dioxide on treatment with 10% chloroplatinic acid. The chloroplatinate of II is formed, melting at 215°. With two equivalents of silver carbonate biscarboxymethyltrimethylammonium betaine IX is obtained in solution, the existence of which can only be inferred from the fact that on acidification with hydrobromic acid, carbon dioxide is liberated and only glycine betaine hydrobromide remains on subsequent total evaporation of the solution, dec. 213.5°.

Reaction of Carbethoxymethyltrimethylammonium Bromide (II) with Ammonia.—The addition of the ester II to liquid ammonia resulted in formation of the corresponding amide at once, m.p. 202° (lit. 202–203°).

Enolization of Biscarbethoxymethyltrimethylammonium Bromide (VII).—The compound VII can be shown to enolize slowly in a well stirred aqueous solution, when one equivalent of 0.01 *N* base is suddenly added to it. A slow drift in *p*H meter reading is observable. If the base is added in smaller portions, each addition of base results in a temporarily high *p*H reading which then, however, slowly drops. The drift ceases completely, once one equivalent of base has been added. Hydrolysis and consequent loss of the ester under investigation is unimportant enough in 0.01 *N* base, so as not to interfere appreciably with the study.

When acid is next added to the basic solution, the *p*H remains low for a short time with a gradual upward drift causing adjustment to a more basic *p*H, since VII is neutral in aqueous solution.

That these drift phenomena are due to a slow chemical change brought about by compound VII and are not inherent in the apparatus or technique is clearly shown by the fact that mixing 0.01 *N* hydrochloric acid and 0.01 *N* sodium hydroxide solution produces an instantaneous and stable change on the *p*H meter reading, which is quite unlike the enolizing system just described.

BALTIMORE, MARYLAND

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(9) E. Strack and K. Foersterling, *Ber.*, **76B**, 21 (1943).